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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,767	ERIKSON ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *6-9* is/are allowed.

6)☐ Claim(s) *1,4,5,8,10-17,29-40,42,43,45,47 and 70* is/are rejected.

7)☒ Claim(s) *2,3,18-28,41,44 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/4/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 27, 2004 has been entered. Claims 1, 23 and 24 have been amended. Claims 1-47 are pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 7, 8, 10-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 7 and 8 are indefinite at the recitation of "free nucleobase" because the term has not been clearly defined in the specification and it cannot be determined what constitutes a free nucleobase. For example, does "free nucleobase" means that an extra nucleobase is added to the blocking agent, or does it mean that the nucleobase is different or distinct from the nucleobases of the target and/or probe, or does the term "free nucleobase" means that the base is incapable of base-pairing or hybridizing to the target and/or probe? Additionally, if the "free nucleobase" is to be interpreted as an extra base, how can the free nucleobase be the only nucleobase of the blocking agent? Clarification is required as to what constitutes a "free nucleobase" in the context of the claimed invention.

(b) Claims 10-17 are confusing at the recitation of "wherein at least one nucleobase is provided in a quantity that is 1-200% of a number of the probe or number of the target nucleobase" because it cannot be determined if reference is being made to a molar concentration or if reference is being made to a length limitation of the nucleobases or if reference is being made to the amount of nucleobases capable of complementarity between the nucleobases of the blocking agent, probe and target. Clarification is required as to what is meant by "a quantity of at least one nucleobase".

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1, 4, 5, 29-31, 39, 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Becker et al. (6,130,038, effective filing date, July 1996). Regarding claim 1, Becker et al. teach a method of forming a complex, said method comprising mixing a probe containing probe nucleobase with a target containing target nucleobase under hybridizing conditions, wherein at least one blocking agent (modifying agent) comprising at least one nucleobase is conjugated to said probe and not to said target prior to hybridizing said probe with said target, wherein said conjugation enhances avidity and specificity of said hybridizing (col. 9, lines 42-67 to col. 10, lines 1-25).

Regarding claim 4, Becker et al. teach the method of claim 1, wherein said at least one blocking agent contains up to five nucleobases (col. 8, lines 53-63 and col. 21, lines 42-48).

Regarding claim 5, Becker et al. teach the method of claim 1, wherein said at least one blocking agent contains up to two nucleobases (col. 8, lines 53-59).

Regarding claim 29, Becker et al. teach the method of claim 1, further comprising detecting said complex (col. 11, lines 28-46; col. 12, lines 8-26 and col. 22, lines 46-47).

Regarding claim 30, Becker et al. teach the method of claim 1, wherein said complex is formed with at said target is bound to a substrate (col. 12, lines 12-17).

Regarding claim 31, Becker et al. teach the method of claim 29, wherein said complex is detected by a change in a signal associated with a label (col. 2, lines 44-53)

Regarding claim 39, Becker et al. teach the method of claim 31, wherein said label is added free in solution to said test medium such that it is capable of binding to the desired nucleic acid (col. 3, lines 35-40 and 12, lines 56-67).

Regarding claim 47, Becker et al teach the method of claim 1, wherein the probe and the target hybridizes in accordance with a homogenous medium (col. 17, lines 34-45).

Therefore, Becker et al. meets all of the claimed limitations of claims 1, 4, 5, 29-31, 39, 47 of the instant invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 32-34, 36-38, 40, 43, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al as previously applied above in view of Heller (US 6,048,690, May 1997). Regarding claims 32-33, Becker et al teach a method of forming a complex between a probe containing probe nucleobase and a target containing target nucleobases, comprising mixing said probe and said target under hybridizing conditions, wherein at least one blocking agent (helper oligonucleotide) comprising at least one nuclease is conjugated to said probe prior to hybridizing said probe to said target and wherein said conjugation enhances avidity and/or specificity of said hybridizing. The method of Becker et al. differs from that of the claimed invention in that Becker et al do not expressly teach wherein in said method the complex is detected by analyzing an electronic characteristic of said complex.

Heller et al teach a method for hybridization analysis by analyzing an electronic characteristic of the hybridization sample (abstract and col. 1, lines 44-55). Heller et al teach wherein the method comprises providing a target comprising at least one nucleic acid sequence; providing a probe comprising a nucleic acid sequence; mixing the probe and the target to a hybridization medium to provide a complex, adding to the complex a label wherein said label is

an environmental sensitive emission label such as a chromophore or fluorophore or luminescent molecule or moiety or metal chelate or enzyme or peptide or amino acid (col. 6, lines 57-59); subjecting the hybridization product and label to a varying electrophoretic force, monitoring the emission from the label and analyzing the monitored emission to determine the electronic fluorescent perturbation effect (abstract and 5, lines 59-67 to col. 6, lines 1-9, which is a rise or spike in fluorescent intensity prior to dehybridization of a fluorescent labeled probe from a capture sequence attached to a microlocation test tube (col. 4, lines 62-66). Heller et al further teach that this method is a powerful analytical tool for DNA hybridization analysis, particularly for the near instantaneous, e.g., less than one minute, and especially less than 5 seconds, discrimination of match/mismatched DNA hybrids and is also useful for novel DNA sequencing applications (col. 5, lines 16-21).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to have been motivated to have modified the method of forming a complex as taught by Becker et al to encompass detection of the complex by analyzing an electronic characteristic as taught by Heller et al. One of ordinary skill in the art would have been motivated to do so for the advantages taught by Heller et al that a method, such as a fluorescent perturbation effect, which utilizes electron power (current and voltage) as described is a powerful tool for DNA hybridization analysis, particularly for the near instantaneous, e.g., less than one minute, and especially less than 5 seconds, discrimination of match/mismatched DNA hybrids and is also useful for novel DNA sequencing applications.

Regarding claim 34, Heller et al teach the method of claim 29, wherein the method of detecting is conducted in a test medium under a varied condition, wherein said varied conditions

is a changed in a electric current and change in an electrical property (col. 7, lines 14-16 and col. 10, lines 63-67 to col. 11, line 10, see also Example 3).

Regarding claim 36, Heller et al teach the method of claim 29, wherein said electrical property is electrical conductance (col. 10, lines 63-65).

Regarding claim 37, Heller et al teach the method of claim 34, wherein said electrical property is amplitude of signal propagated in said transmission line in said test medium (col. 9, lines 1-6).

Regarding claim 38, Heller et al teach the method of claim 34, wherein said complex is detected under serially varied conditions (col. 7, lines 14-16 and col. 10, lines 63-67 to col. 11, line 10, see also Example 3).

Regarding claim 40, Heller et al teach the method of claim 29, further comprising detecting a signal from a label wherein said signal is correlated to a binding affinity between said probe said target; varying conditions of a test medium and detecting a subsequent signal and comparing the first signal and subsequent signal (see examples 3 and 4).

Regarding claim 43, Becker teaches a method of claim 1, wherein binding may be facilitated by intercalation (col. 10, lines 2-3).

Regarding claims 42 and 45, Becker teaches the method of claim 1, probes hybridizes to a complementary target sequence suggesting a Watson Crick motif to form a triplex (col. 10, lines 2-11).

9. Claim 35 are rejected under 35 U.S.C. 103(a) ass being unpatentable over Becker et al as previously applied above in view of Wu et al (US 5,846,729, filing date July 1, 1997). Regarding claim 35, Becker et al teach a method of forming a complex between a probe

containing probe nucleobases and a target containing target nucleobases, comprising mixing said probe and said target under hybridization conditions, wherein at least one blocking agent (helper oligonucleotide) comprising at least one nucleobase is conjugated to said probe prior to hybridizing said probe to said target and wherein said conjugation enhances an avidity and/or specificity of said hybridizing.

The method of Becker et al differs from that of the claimed invention in that the Becker et al do not teach wherein in said method the complex is detected in a test medium under varied conditions wherein said varied condition is a change in a number of photons in the test medium. Becker et al additionally do not teach wherein a laser bean is applied t said test medium to effect said change in the number of photons.

Wu et al teach a method of forming a hybridization complex between a target nucleic acid and probe in a test medium and detecting said hybridization complex by applying a laser beam to the hybridization sample which is capable of effecting changes in the number of photons and measuring signal intensity (col. 3, lines 29044, col. 5, lines 57-58, col. 6, lines 5-51). Wu et al teach that by using this method for detecting hybridization, no separation of the hybridization complex from the uncomplex probes is necessary prior to signal determination (col. 6, lines 52-54). Wu et al teach that additionally that nucleotide sequence information can be determined by monitoring a change in the overall signal intensity, which is a function of hybridization and hybridization efficiency (col. 6, lines 62-65).

Therefore, in view of the foregoing, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to have been motivated to have modified the method of detecting a hybridization complex as taught by Hogan et al to encompass detection of

the complex by applying a laser beam capable of effecting change in the number of photons in a test medium as taught by Wu et al. One of ordinary skill in the art would have been motivated to do for the advantages taught by Wu et al that the method, wherein a laser beam is applied to detect a hybridization complex, requires no separation of unhybridized probes from the hybridization complex prior to signal detection and for the advantages that sequence information can be determined by monitoring a change in the overall signal intensity which is a function of hybridization and hybridization efficiency.

Conclusions

10. Claims 1, 4, 5, 7-8, 10-17, 29-40, 42, 43, 45, 47 are not allowed. Claims 2, 3, 18-28, 41, 44, and 46 are objected. Claims 6-9 contain allowable subject matter.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Cynthia Wilder

CYNTHIA WILDER
PATENT EXAMINER

7/20/2004